#18
10/31/02
C. Styles

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jacques DUMAS et al. Examiner: D. Rao

Serial No.: 09/472,232 Group Art Unit: 1624

Filed: December 27, 1999

Title: INHIBITION OF RAF KINASE USING ARYL AND HETEROARYL SUBSTITUTED HETEROCYCLIC UREAS

I hereby certify that this correspondence is being deposited with the U.S. Postal Services as First Class Mail in an envelope addressed to Assistant Commissioner for Patents Washington, D.C. 20231 On: October 21, 2002
Name: Richard J. Traverso
SIGNATURE
DATE: 10/21/02

BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Further to the Notice of Appeal filed on April 19, 2002, herewith are three copies of Appellants' Brief on Appeal. Please debit Deposit Account No. 13-3402 for the statutory fee of $320.00 and debit or credit deposit account No. 13-3402 for any under or overpayment of this fee. Two copies of this page are attached for this purpose. A request for a four month extension of the term and check for the fee of $390.00 accompany this Brief on Appeal.

I. REAL PARTY IN INTEREST

The application is assigned of record to Bayer Corporation, 100 Bayer Road, Pittsburgh, Pennsylvania 15205, which is the real party in interest herein.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to appellant or appellant's legal representative which will directly affect or be directly affected by or have any bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

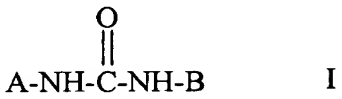
Claims 1-25 are pending. Claims 11-14 were withdrawn from consideration. Claims 1-10 and 15-25 are the subject of this appeal.

IV. STATUS OF AMENDMENTS AFTER FINAL

This brief has been filed after a second non-final office action. The claims were amended on June 19, 2002 and the claims in the Appendix reflect these amendments.

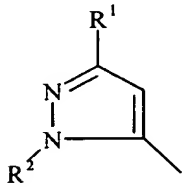
V. SUMMARY OF THE INVENTION

The present invention provides compounds of formula I below which are inhibitors of the enzyme raf kinase. The invention also provides a method for treating a raf mediated disease state in humans or mammals comprising administering a compound of formula I.

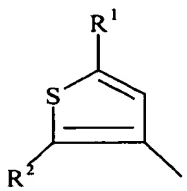


I

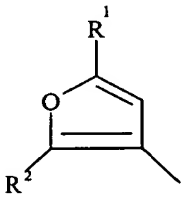
In formula I, A is a heteroaryl selected from the group consisting of



,



and



with R^1 selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl and R^2 selected

from C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl. Substituent B of formula I is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur.

VI. ISSUES

1. Whether the Declaration is defective.
2. Whether Claims 15-23 are supported by the disclosure as required under 35 U.S.C. §112, first paragraph.
3. Whether claim 23 is sufficiently definite to satisfy 35 U.S.C. § 112, second paragraph.
4. Whether Claims 1-10 and 24-25 are properly rejected under 35 U.S.C. § 102(e) based on Regan et al. (U.S. 6,080,763).
5. Whether Claims 1-10 and 24-25 are properly rejected under 35 U.S.C. § 103(a) based on Regan et al. (U.S. 6,080,763).
6. Whether Claims 1-5,7-10 and 24-25 are properly rejected under 35 U.S.C. § 103(a) based on Creswell et al. (U.S. 5,162,360).
7. Whether claims 1-10, 17-20 and 24-25 are properly rejected under 35 U.S.C. § 112, first paragraph, as containing new matter.
8. Whether claims 1-10 and 15-25 are properly rejected under 35 U.S.C. § 112, first paragraph as not enabled by the specification for the full scope of substituents "B" of formula I.
9. Whether claims 1-10 and 15-25 are properly rejected under 35 U.S.C. § 112, second paragraph as indefinite.
10. Whether Claims 15-23 are properly rejected under 35 U.S.C. § 103(a) based on Regan et al. (U.S. 6,080,763) in view of Bruder et al (J.Vir. 1997).

VII. GROUPING OF CLAIMS

Claims 1-10 and 15-25 do not stand or fall together for the reasons indicated below.

VIII. ARGUMENTS

1. Whether the Declaration is defective.

A new Oath/Declaration was submitted on October 31, 2001 which properly identifies the serial number of this application as well as the provisional application as 60/135,502. The first paragraph of the specification has been amended to correct the reference to the serial number of the provisional application.

2. Whether Claims 15-23 are supported by the disclosure as required under 35 U.S.C. §112, first paragraph

The inhibition of raf kinase as a means for treating diseases dependent on the ras protein signal transduction cascade is known in the art, as discussed in the publications cited in the specification. The specification identifies the compounds recited in claims 15-23 as raf-kinase inhibitors and provides guidance (e.g. dosage ranges and methods of administration) on pages 14-17 to one skilled in the art how to achieve such activity within a host.

3. Whether claim 23 is sufficiently definite to satisfy 35 U.S.C. § 112, second paragraph II. .

Applicants have amended claim 23 to recite "raf kinase" to overcome the rejection under 35 U.S.C. § 112, second paragraph. This rejection is now moot.

4. Whether Claims 1-10 and 24-25 are properly rejected under 35 U.S.C. § 102(e) based on Regan et al. (U.S. 6,080,763).

Amended claims 1-10 and 24-25 define compounds which have an aryl/heteroaryl substituted heteroaryl group on one side of the urea functional group and a bridged aromatic

group on the other side of the urea functionality urea. These claims do not encompass the compound N-(3-t- butyl-1-(4-methylphenyl)pyrazol-5-yl)-N'-(2,4-dichlorolphenyl)urea disclosed by Regan et al. in the provisional application 60/064,102 (the priority document to U.S. 6,080,763). Therefore, there is no longer a basis for the rejection of these claims under 35 USC §102(e).

5. Whether Claims 1-10 and 24-25 are properly rejected under 35 U.S.C. § 103(a) based on Regan et al. (U.S. 6,080,763).

Amended claims 1-10 and 24-25 now define compounds which have an aryl/heteroaryl substituted heteroaryl group on one side of the urea functional group and a bridged aromatic group on the other side of the urea functionality urea. The claimed compounds are structurally unobvious over the compound N-(3-t- butyl-1-(4-methylphenyl)pyrazol-5-yl)-N'-(2,4-dichlorolphenyl)urea disclosed by Regan et al. in the provisional application 60/064,102 on page 9. Regan et al. provides no hint or suggestion to modify this compound to incorporate a bridged aromatic group on the 2,4-dichlorophenyl ring.

6. Whether Claims 1-5,7-10 and 24-25 are properly rejected under 35 U.S.C. § 103(a) based on Creswell et al. (U.S. 5,162,360).

Claims 1-5, 7-10 and 24-25 are now directed to compounds wherein "B" of Formula I is a bridged aromatic group and "A" of formula I is a heteroaryl group substituted by an aryl/heteroaryl group (R^2) as well as an alkyl/cycloalkyl group (R^1). The disclosure of Creswell et al. is so broad as to provide no hint or suggestion of preparing such compounds. In maintaining this rejection, a comparison of heteraryl group "A" to formula (8) at column 3 of Creswell is made. However, this is only a portion of there the structure which defines the compounds claimed herein. There is no suggestion or motivation to match this partial structure with structure consistent with "B" of formula I herein. In fact, none of the specific urea compounds disclosed in the Examples of Creswell have a bridged aromatic group consistent with "B" herein.

7. Whether claims 1-10, 17-20 and 24-25 are properly rejected under 35 U.S.C. § 112, first paragraph, as containing new matter.

The specification has been amended to provide support for the definition of Ar in the claims as a 5-10 member aromatic structure. This amendment does not add new matter in that the "5-6 member" aromatic structures, for Ar are said to be preferred and the '5-10 member" aromatic structures for Ar were described in the original claims.

8. Whether claims 1-10 and 15-25 are properly rejected under 35 U.S.C. § 112, first paragraph as not enabled by the specification for the full scope of substituents "B" of formula I.

In rejecting claims 1-10 and 15-25 under 35 U.S.C. § 112, first paragraph, it is alleged the specification provides no disclosure on how the starting materials are obtained to prepare the claimed compounds. Applicants submit the "General Method for Substituted Aniline Synthesis" described on page 23 provides sufficient guidance for the preparation of starting materials that form group B of formula I when reacted with an aryl isocyanate. In addition, the general methods described on pages 10-13 outline how to synthesize aryl amine starting materials by the formation of nitroaryls followed by reduction. Furthermore, the publications listed on pages 10 and 11, which are incorporated in the specification by reference, describe methods for synthesizing aryl amine starting materials. Therefore, the specification is clearly enabling for the complete scope of compounds defined in claims 1-10 and 15-25.

9. Whether claims 1-10 and 15-25 are properly rejected under 35 U.S.C. § 112, second paragraph as indefinite.

a) Applicants maintain that the open meaning of the term "containing" in the phrase "containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur" within definition of B is appropriate since it is used in the context of describing members of the aromatic structure, which clearly additionally includes carbon.

b) Applicants maintain it is appropriate for Claim 17 to include the 3 ring formula

with the substituent R^5 as defined in Claim 17. This 3-ring formula is consistent with the scope of "B" defined in claim 15 in that it includes the substituents of X defined in Claim 15 (C_1-C_{10} alkyl, alkenyl, cycloalkyl, etc.) which can appear on B, plus "hydrogen," which is consistent with B being unsubstituted. But for the substituent "hydrogen", R^5 is not broader than X.

c) The formula in Claim 18 has been amended to specify values for the subscript of X within the scope of "n-1". The values for the original variable "n" ranged from 0-3. With the substituent Y-Q_1-Z_{n1} present on Q, the maximum number of "x" substituents is 2.

d) The language the examiner refers to in claim 18 (and claim 4) has been amended so that "Q_1" is consistent with "Ar."

e) The language the examiner refers to in claim 19 (and amended claim 5) regarding "Y-Ar is phthalimidinyl" has been cancelled.

f) Claim 15 has been amended to recite a host.

10. Whether Claims 15-23 are properly rejected under 35 U.S.C. § 103(a) based on Regan et al. (U.S. 6,080,763) in view of Bruder et al (J.Vir. 1997).

The publication by Bruder et al. discloses that adenovirus infection activates Raf-1 and MAPK pathways and that IL-8 production is induced by adenovirus infection. Bruder et al. also discloses that the raf kinase inhibitor, forskolin, inhibited the adenovirus infection-induced MAPK activation and IL-8 production.

Bruder et al. acknowledges that no link between inhibiting raf kinase activity and treating inflammatory diseases is shown by the following statements on page 402, lines 26-28 and 57-60.

"The finding that adenovirus infection activates the raf/MAPK signal pathway raises the possibility that activation of this pathway is necessary for efficient adenovirus infection." (emphasis added) lines 26-28 and

"Alternatively, it is possible that activation of this pathway is not important for efficient infection and that it is a side effect of the infection" lines 57-60.

Assuming that the possibility presented by Bruder et al. is confirmed, i.e., that activation of raf pathway is necessary for efficient adenovirus infection, there is no hint or suggestion the

compounds of Regan would be effective to inhibit raf kinase. Bruder et al., provides no hint or suggestion that compounds which inhibit cytokine production involved in inflammation necessarily inhibit raf kinase. Therefore, the methods claimed herein which employ an amount of compounds of Formula I effective to inhibit raf kinase are not obvious in view of these combined teachings.

IX. CONCLUSION

Based on the above remarks, Appellants submit that the claims are in a form with satisfies 35 U.S.C. § 112, and are novel and unobvious in view of the cited references such that the rejections discussed above should be reversed.

Respectfully submitted,

Richard J. Traverso, Reg. No. 30,505
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

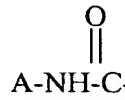
Attorney Docket No.: BAYER 9C1

Date: **October 21, 2002**

RJT/lvb
K:\Bayer\9\c1\Brief.dot

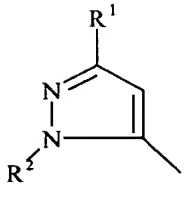
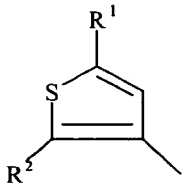
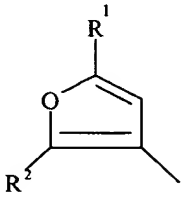
APPENDIX

1. A compound of formula I or a pharmaceutically acceptable salt thereof



A-NH-C-NH-B I

wherein A is a heteroaryl selected from the group consisting of



and


wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is an up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, substituted by -Y-Ar and optionally substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-2 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkoxyl, substituted C_3-C_{10} cycloalkyl, and substituted C_4-C_{23} alkheteroaryl -Ar;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-

halosubstituted C_1-C_{10} alkyl, up to perhalosubstituted C_2-C_{10} alkenyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is -O-, -S-, -N(R^5)-, -(CH_2)-$_m$, -C(O)-, -CH(OH)-, -(CH_2)$_m$O-, -NR^5C(O)N$R^5R^{5'}$-, -NR^5C(O)-, -C(O)NR^5, -O(CH_2)$_m$-, -(CH_2)$_m$S-, -(CH_2)$_m$N(R^5)-, -O(CH_2)$_m$-, -CHX^a-, -CX^a_2-, -S-(CH_2)$_m$- and -N(R^5)(CH_2)$_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -C(O)NR^5, -NO_2, -OR^5, -SR^5, -N$R^5R^{5'}$, -NR^5C(O)O$R^{5'}$, -C(O)R^5, NR^5C(O)$R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -OR^5, -SR^5, -NO_2, -N$R^5R^{5'}$, -NR^5C(O)$R^{5'}$ and -NR^5C(O)O$R^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

wherein n = 0-3 and each V is independently selected from the group consisting of -CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -OR^5, -SR^5, -N$R^5R^{5'}$, -C(O)R^5, -OC(O)N$R^5R^{5'}$, -NR^5C(O)O$R^{5'}$, -SO_2R^5, -SOR^5, -NR^5C(O)$R^{5'}$, -NO_2, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

where if V is a substituted group, it is substituted by one or more substituents

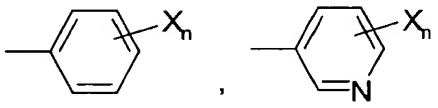
independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^5$, -$NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and -NO_2;

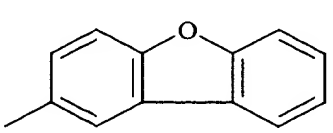
wherein R^5 and $R^{5'}$ are each independently as defined above.

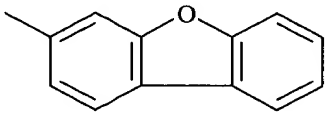
2. A compound of claim 1, wherein R^2 is substituted or unsubstituted phenyl or pyridinyl, and the substituents for R^2 are selected from the group consisting of halogen, up to per-halosubstitution and V_n, wherein n = 0-3, and each V is independently selected from the group consisting of substituted and unsubstituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, -NO_2, -NH_2, -C(O)-C_{1-6} alkyl, -C(O)N-(C_{1-6} alkyl)$_2$, -C(O)NH-C_{1-6} alkyl, -O-C_{1-6} alkyl, -NHC(O)H, -NHC(O)OH, -N(C_{1-6} alkyl)C(O)-C_{1-6} alkyl, -N-(C_{1-6} alkyl)C(O)-C_{1-6} alkyl, -NHC(O)-C_{1-6} alkyl, -NHC(O)O-C_{1-6} alkyl, -S(O)-C_{1-6} alkyl and -SO_2-C_{1-6} alkyl,

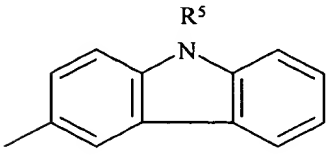
wherein if V is a substituted group, it is substituted by one or more halogen, up to per-halosubstitution.

3. A compound of claim 2, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of

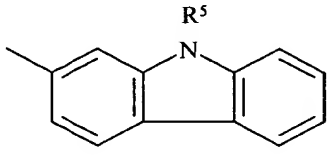








and



;

which is substituted or unsubstituted by halogen, up to per-halosubstitution, and wherein

n = 0-3 and

each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, and substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is - O-, -S-, $-N(R^5)-$, $-(CH_2)_m-$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a{}_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

m = 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halo substitution and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$.

4. A compound of claim 1, wherein

Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a_2$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$, and

X^a is halogen.

5. (Amended) A compound of claim 4, wherein

Ar is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, unsubstituted or substituted by halogen, up to per-halo substitution, and

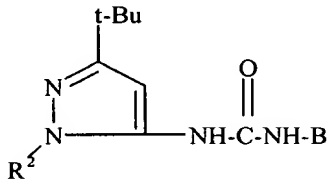
Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

6. A compound of claim 1, wherein R^1 is t-butyl and R^2 is unsubstituted or substituted phenyl.

7. A compound of claim 4, wherein Ar is phenyl or pyridinyl, Y is –O-, -S- or $-CH_2-$, and X and Z are independently Cl, F, NO_2 or CF_3.

8. A compound of claim 7, wherein R^1 is t-butyl.

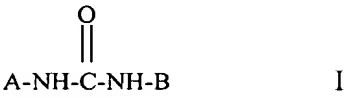
9. A compound of claim 1 of the formula



wherein B and R^2 are as defined in claim 1.

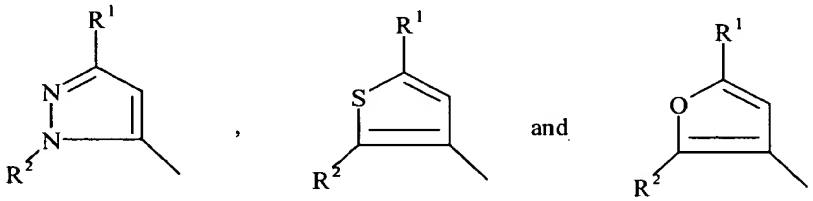
10. A compound of claim 9, wherein R^2 is selected from substituted and unsubstituted members of the group consisting of phenyl and pyridinyl, wherein if R^2 is a substituted group, it is substituted by one or more of the substituents selected from the group consisting of halogen and W_n, wherein n = 0-3, and W is selected from the group consisting of $-NO_2$, $-C_{1-3}$ alkyl, $-NH(O)CH_3$, $-CF_3$, $-OCH_3$, -F, -Cl, $-NH_2$, $-SO_2CH_3$, pyridinyl, phenyl, up to per-halosubstituted phenyl and C_1-C_6 alkyl substituted phenyl.

15. (Amended) A method for the treatment of disease mediated by raf kinase, comprising administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof to a host in need thereof:



I

wherein A is a heteroaryl selected from the group consisting of



wherein R^1 is selected from the group consisting of C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl;

B is a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n,

wherein n is 0-3 and each X is independently selected from the group consisting of –CN, CO_2R^5, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_{1-10}-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14}

aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted $C_{2\text{-}10}$-alkenyl, substituted $C_{1\text{-}10}$-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

where X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, $C_{2\text{-}10}$-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted $C_{2\text{-}10}$-alkenyl , up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and up to per-halosubstituted C_3-C_{13} heteroaryl, wherein Y is - O-, -S-, $-N(R^5)$-, $-(CH_2)_m$-, -C(O)-, -CH(OH)-, $-(CH_2)_mO$-, $-(CH_2)_mS$-, $-(CH_2)_mN(R^5)$-, $-O(CH_2)_m$-, $-CHX^a$-, $-CX^a{}_2$-, -S-$(CH_2)_m$- and $-N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, $-C(O)R^5$, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl;

wherein if Z is a substituted group, it is substituted by the one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NO_2$, $-NR^5R^{5'}$, $-NR^5C(O)R^{5'}$ and $-NR^5C(O)OR^{5'}$, and

wherein R^2 is C_6-C_{14} aryl, C_3-C_{14} heteroaryl, substituted C_6-C_{14} aryl or substituted C_3-C_{14} heteroaryl,

wherein if R^2 is a substituted group, it is substituted by one or more substituents

independently selected from the group consisting of halogen, up to per-halosubstitution, and V_n,

wherein n = 0-3 and each V is independently selected from the group consisting of -CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, -$OC(O)NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)OR^{5'}$, -SO_2R^5, -SOR^5, -$NR^5C(O)R^{5'}$, -NO_2, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{24} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{24} alkheteroaryl,

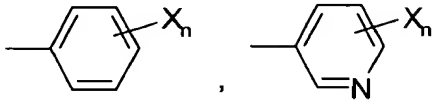
where V is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, -CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^5$, -$NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5C(O)R^{5'}$, -$NR^5C(O)OR^{5'}$ and -NO_2,

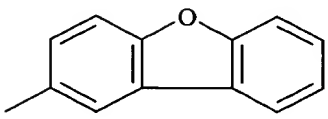
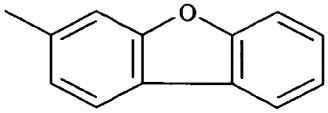
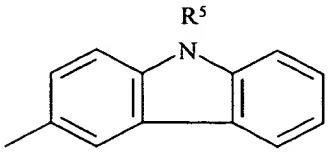
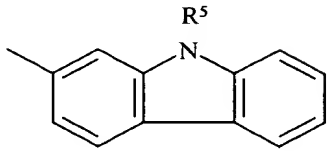
wherein R^5 and $R^{5'}$ are each independently as defined above.

16. A method as in claim 15, wherein R^2 is selected from substituted or unsubstituted members of the group consisting of phenyl and pyridinyl, and the substituents for R^2 are selected from the group consisting of halogen, up to per-halosubstituition and V_n, wherein n = 0-3, and each V is independently selected from the group consisting of substituted and unsubstituted C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_6-C_{10} aryl, -NO_2, -NH_2, -$C(O)$-C_1-$_6$ alkyl, -$C(O)N$-(C_1-$_6$ alkyl)$_2$, -$C(O)NH$-C_1-$_6$ alkyl, -O-C_1-$_6$ alkyl, -$NHC(O)H$, -$NHC(O)OH$, -$N(C_1$-$_6$ alkyl$)C(O)$-C_1-$_6$ alkyl, -N-(C_1-$_6$ alkyl$)C(O)$-C_1-$_6$ alkyl, -$NHC(O)$-C_1-$_6$alkyl, -$NHC(O)O$-C_1-$_6$ alkyl, -$S(O)$-C_1-$_6$ alkyl and -SO_2-C_1-$_6$ alkyl,

wherein if V is a substituted group, it is substituted by one or more halogen, up to per-halosubstitution.

17. A method as in claim 15, wherein B is up to a tricyclic aromatic ring structure selected from the group consisting of



which is substituted or unsubstituted by halogen, up to per-halosubstitution, and wherein

n = 0-3 and

each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_3-C_{13} heteroaryl, C_4-C_{23} alkheteroaryl, and substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_4-C_{23} alkheteroaryl and -Y-Ar;

wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)R^5$, $-C(O)NR^5R^{5'}$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NO_2$, $-NR^5C(O)R^{5'}$, $-NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_6-C_{14} aryl and

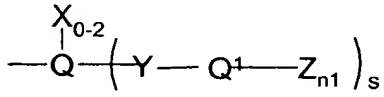
up to per-halosubstituted C_3-C_{13} heteroaryl,

wherein Y is - O-, -S-, -N(R^5)-, -(CH_2)-$_m$, -C(O)-, -CH(OH)-, -(CH_2)$_m$O-, -(CH_2)$_m$S-, -(CH_2)$_m$N(R^5)-, -O(CH_2)$_m$-, -CHX^a-, -CX^a_2-, -S-(CH_2)$_m$- and -N(R^5)(CH_2)$_m$-,

m = 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur which is unsubstituted or substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -C(O)R^5, -NO_2, -OR^5, - SR^5, - N$R^5R^{5'}$, -NR^5C(O)O$R^{5'}$, -NR^5C(O)$R^{5'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, -CO_2R^5, -C(O)N$R^5R^{5'}$, -OR^5, -SR^5, -NO_2, -N$R^5R^{5'}$, -NR^5C(O)$R^{5'}$ and -NR^5C(O)O$R^{5'}$.

18. (Amended) A method of claim 15, wherein B is



wherein

Y is selected from the group consisting of –O-, -S-, -CH_2-, -SCH_2-, -CH_2S-, -CH(OH)-, -C(O)-, -CX^a_2, -CX^aH-, -CH_2O- and -OCH_2-,

X^a is halogen,

Q is a six member aromatic structure containing 0–2 nitrogen, unsubstituted or substituted by halogen, up to per-halosubstitution;

Q^1 is a mono- or bicyclic aromatic structure of 5-10 members with 3 to 10 carbon atoms and 0-2 members of the group consisting of N, O and S, unsubstituted or substituted by halogen up to per-halosubstitution,

X, Z, and n1 are as defined in claim 15, and s = 0 or 1.

19. (Amended) A method as in claim 18, wherein

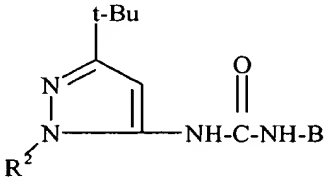
Q is phenyl or pyridinyl, unsubstituted or substituted by halogen, up to per-halosubstitution,

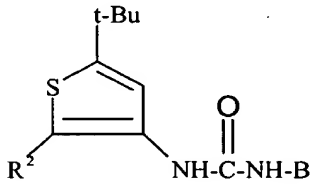
Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, and

Z and X are independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, C_3-C_6-cycloalkyl and C_6-C_{10}-aryl, wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

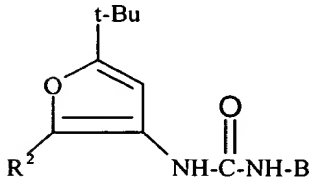
20. A method as in claim 18, wherein Q is phenyl, Q^1 is phenyl or pyridinyl, Y is –O-, -S- or $-CH_2$-, and X and Z are independently Cl, F, NO_2 or CF_3.

21. A method as in claim 15, which comprises administering a compound of one of the formulae





or



wherein B and R^2 are as defined in claim 15.

22. A method as in claim 21, wherein R^2 is selected from substituted and unsubstituted members of the group consisting of phenyl or pyridinyl, wherein if R^2 is a substituted group, it is substituted by one or more substituents selected from the group consisting of halogen and W_n, wherein n = 0-3, and W is selected from the group consisting of $-NO_2$, $-C_{1-3}$ alkyl, $-NH(O)CH_3$, $-CF_3$, $-OCH_3$, -F, -Cl, $-NH_2$, $-SO_2CH_3$, pyridinyl, phenyl, up to per-halosubstituted phenyl and C_1-C_6 alkyl substituted phenyl.

23. (Amended) A method as in claim 15, comprising administering an amount of compound of formula I effective to inhibit raf kinase.

24. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition comprising a compound of claim 2 and a pharmaceutically acceptable carrier.